REMARKS

Entry of this Amendment is proper under 37 C.F.R. 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not introduce any new claims; does not raise any new issue requiring further search and/or consideration because the amendments amplify issues previously discussed throughout prosecution, and places the application in better form for an appeal should an appeal be necessary.

As noted in the Office Action, claims 32, 36, 38, 40, 44, 46, 48, 49, 53-56, 62, 64, 65, 69, 71-75, 79, and 80 are pending. Claims 53-56 and 79-80 are amended herein to remove reference to prevention. Thus, no prohibited new matter is presented herein. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment.

Rejections Under 35 U.S.C. § 103

Claims 32, 36, 38, 53 and 54 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Lowy et al. (U.S. Patent No. 5,618,536) ("Lowy"), Hagensee et al. (*Journal of Virology*, 1993; 67 (1): 315-322) ("Hagensee"), Borysiewicz et al. (*Lancet*, June, 1996; 347: 1523-1527) ("Borysiewicz"), Galloway (*Infectious Agents and Disease*, 1994; 3: 187-193) ("Galloway"), and Meyer et al. (*Journal of Virology*, 1991; 72: 1031-1038) ("Meyer"), as further evidenced by Boursnell et al. (U.S. Patent No. 5,719,054) ("Boursnell").

For a *prima facie* case of obviousness, the following three requirements must be met. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or

incentive that would have motivated the skilled artisan to modify a reference or to combine the reference with another reference. Second, the proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Third, the prior art reference must teach or suggest all the limitations of the claims. The teachings or suggestions, as well as the expectation of success, must come from the prior art and not from applicant's disclosure. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); and *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

Applicants respectfully submit that the cited references, alone or in combination, do not meet the requirements for a *prima facie* case of obviousness. The Office maintains that the skilled artisan would have been motivated to combine the prophylactic L1 and L2 papillomavirus polypeptides of Lowy and Galloway with the therapeutic E6 and E7 polypeptides of Galloway, Lowy and Berysiewicz into a single composition, in order to treat or prevent papillomavirus infection. Thus, the Office argues that it is obvious that a composition comprising L1, L2, E6 and E7 papillomavirus polypeptides would be therapeutic and prophylactic.

However, Applicants note that the presently pending claims are not directed to a composition consisting of the combination of L1, L2, E6 and E7 papillomavirus polypeptides. Instead, the claimed composition requires a MVA vector that expresses L1, L2, E6 and E7 under the control of independent regulatory elements. The MVA vector and the independent expression of the papillomavirus polypeptides are key elements of the present composition, as currently claimed.

None of the cited references, taken in combination, discloses or even suggests these features of the present claims. Hagensee discloses the use of L1 and L2 papillomavirus genes for prophylactic purposes. Borysiewicz and Boursnell disclose the use of E6 and E7 papillomavirus genes for therapeutic purposes. Galloway disclose that the early papillomavirus polypeptides can be used for therapeutic purposes or the late papillomavirus polypeptides for prophylactic purposes (*see* Abstract). In fact, Galloway specifically describes experimental work involving either late papillomavirus polypeptides recombinantly produced as fusion proteins (page 190, second column), or individual early papillomavirus polypeptide (page 191, from the second sentence to the end of the first paragraph of the first column).

The only cited reference suggesting combining both early and late polypeptides in a single composition is Lowy. However, Lowy sets forth a method of preventing or treating papillomavirus infection relying on the use of chimeric virus-like particles (VLP). These chimeric VLPs are composed of self-assembled L1, polypeptide and a fusion product between L2 and an early papillomavirus polypeptide. The incorporation of the E7 polypeptide into the L2 polypeptide results in the appearance of the early epitopes at the surface of the VLP to be amenable to the immune effecter cells. However, this disclosure is in marked contrast to the presently claimed composition, which is directed to un-fused early and late papillomavirus polypeptides expressed from independent promoters in a single MVA vector.

On page 2 of the Office Action, the Office contests Applicants' statement that the VLPs of Lowy mimic the structure and morphology of the virus at issue. The Office states that in their natural context, wild-type papillomavirus virions do not

express or expose early polypeptides, such as E7, on the surface. Applicants note that It is correct that wild-type papilloma virions do not expose early polypeptides such as E6 or E7 at their surface, because these proteins, once synthesized in the infected cell, are targeted to the cell nucleus. Thus they provide for malignant transformation through interaction with cellular proteins involved in the regulation of cell proliferation such as p53 and Rb. However, Applicants submit that the term "mimic" is used in the correct context, meaning "resembling," i.e., the composition of Lowy is based on the administration of viral capsid structures composed of L1 and L2, which further include and expose E7 in order to have the E7 polypeptide amenable to the patient's immune cells. In the absence of fusion in L2, the E7 polypeptide would be masked to the immune system (*e.g.*, trapped into the viral capsid) and thus not capable of eliciting an immune response.

In this respect, the chimeric VLPs of Lowy were shown to elicit neutralizing antibodies that recognize the VLP-exposed E7 polypeptide. However, apart from detecting neutralizing anti-E7 antibodies in immunized animals and demonstrating prophylactic protection against subsequent papillomavirus infection, Lowy fails to demonstrate any therapeutic protection against HPV-induced tumors following administration of the chimeric VLP particles presenting E7 at their surface.

In general, agreement in the art exists that antibodies against the E7 proteins of HPV-16 are frequently found in sera from patients with cervical cancer and that the anti-E7 antibodies rise with tumor stage (*see* Galloway, page 189, first paragraph, second column). Thus, production of anti-E7 antibodies as demonstrated by Lowy is not predictive of therapeutic efficacy.

Applicants submit that there is no expectation of success that the recombinant MVA vector used in the method of the invention can achieve therapeutic protection

against HPV-infection. At most, the skilled person could only have hoped and not expected success in the method of the present invention. The Office never meets any standard other than at best that of "obvious to try", which is not the standard by which a *prima facie* case of obviousness is determined.

Regarding the Galloway reference, the Office states that because Galloway notes the L1 and L2 proteins in the alternative, they are obviously not fused to each other. To this end, Applicants submit that the composition of the invention provides expression of the L1 and L2 polypeptides in a non-fused manner. Applicants note that in the abstract, Galloway discloses that the early papillomavirus polypeptides can be used for therapeutic purposes or the late papillomavirus polypeptides for prophylactic purposes.

This supports the argument that there is no motivation in the cited references, alone or in combination, to combine late and early papillomavirus genes, and especially to use a MVA vector expressing multiple and non-fused papillomavirus polypeptides (*i.e.*, 4 papillomavirus genes expressed from independent control elements). The cited references lead the skilled artisan to insert the sequences encoding the early HPV polypeptides into the coding sequence of the late L2 polypeptide to improve accessibility to the host's immune system and that the expression of multiple genes from independent promoters in a single vaccinia vector could be difficult to achieve.

Regarding Boursnell, the Office states that this reference explicitly discloses un-fused expression of papillomavirus proteins by reference to Figure 26c, column 3, lines 29-35 and column 8, lines 24-37. Applicant draw the Examiner's attention to the legend of Figure 26, indicating that this Figure illustrates a variety of options for arrangement of HPV-16 and HPV-18 E6 and E7 coding sequences in a recombinant

virus vector. Column 3, lines 29-35 provides a recombinant vector which can maintain stably and express part or all of four of the desired gene sequences from HPV-16 and HPV-18. Column 8, lines 24-37 discloses the promoter sequences that may be used to provide expression of the one or more open reading frames inserted in a recombinant virus vector by using a first promoter which controls the expression of the genetic sequences from first open reading frame and one or more further promoters which control the expression of the genetic sequences from one or more further open reading frame. Applicants stress that Boursnell, as referred to by the Office, is very general and encompasses all virus vectors available in the art (*e.g.*, adenovirus, herpes virus, retrovirus, AAV, and the like) that are suitable to express one or more gene sequences.

However, when referring specifically to vaccinia virus vector, Boursnell recognizes that multiple gene expression as independent expression units can be problematic (paragraph bridging columns 9 and 10). The solution provided by Boursnell to obviate the difficulty of expressing multiple genes in a vaccinia virus is to fuse the E6 and E7 coding sequences. The described fusion permits to reduce to two the number of expression cassettes to be inserted in and expressed from the single vaccinia virus vector. This is clearly evident from the statement of Boursnell, "Expression of the desired four gene sequences in the vaccinia virus genome could also be difficult (though not impossible) to achieve as independent expression units, and so the invention provides that instead, the E6 and E7 open reading frames may be fused together." Thus, Boursnell teaches away from the present invention.

Applicants further refer to column 10, lines 56-58 where Boursnell states "For insertion into vaccinia virus, the E6 and E7 genes from each HPV type, are first fused together to form a single continuous OFR". Further, the fusion approach is

perfectly in line with the specification (*see* for example, the paragraph at the bottom of column 5, column 6, and the paragraph at the top of column 7) and the working examples which illustrate a vaccinia virus vector containing two expression cassettes one directing expression of fused HPV-16 E6 and E7 coding sequences and the second one directly expression of fused HPV-18 E6 and E7 coding sequences.

On page 4 of the Office Action, the Office states that Boursnell accounts for the possible difficulty in expressing multiple genes in a vaccinia virus vector, due to extraneous marker sequences. Boursnell does disclose that methods of insertion have been developed to allow elimination of the extraneous marker sequences (column 10, lines 1-8). Yet, contrary to the Office's assertion on page 16 of the Office Action, the method does not eliminate the need for marker genes. Instead, after selection based on the phenotypic property provided by the marker gene product, the marker sequences are eliminated from the recombinant vaccinia genome upon amplification of the recombinant virus. In our opinion, elimination of selection marker sequences is more related to a safety concern (note that it is desirable that the final construct be unable to express potentially harmful gene products such as antibiotic resistance in a human patient) than to expression of multiple genes.

Contrary to the Office's assertions, the independent expression of four different papillomavirus polypeptides in a vaccinia virus vector is not expressly taught by the combination of references cited by the Office. The skilled artisan would not have had any reasonable expectation of expressing four papillomavirus polypeptides in a single vaccinia virus vector under independent regulatory elements.

Applicants further note that vaccinia virus infection is lytic, as mentioned by Borysiewicz (page 1526, second paragraph of the discussion) whereas MVA

infection is abortive (as mentioned by Meyer et al., on page 1031, second column "the host range of this strain [MVA] is severely restricted as it replicates only in CEFs"). These differences in cell infection are likely to be due to the several deletions that have occurred in MVA genome as compared to the lytic vaccinia virus genome, may influence the immune host response to infection. On the basis of these differences, at the time the present invention was made, there was no expectation of success that administration of a MVA vector expressing both early and late papillomavirus polypeptides independently each other would confer an appropriate therapeutic response against HPV infection.

Applicants submit that there is no suggestion or motivation in the cited references or the knowledge generally available to one of ordinary skill in the art to combine the disclosures of the cited references in the manner necessary to arrive with a reasonable expectation of success at a MVA vector coding independently for L1, L2, E6 and E7 papillomavirus polypeptides.

Claim 40 stands rejected under 53 U.S.C. § 103(a) as purportedly unpatentable over Lowy, Hagensee, Borysiewicz, Galloway, and Meyer, as further evidenced by Boursnell and further in view of Crook et al. (*Cell.* 1991; 67: 547-556) ("Crook") and Munger et al. (*EMBO Journal.* 1989; 8: 4099-4105) ("Munger").

Claim 40 is a dependent claim referring back to claim 32. Applicants refer to the comments above, submitted on behalf of the rejection of claim 32. Thus, as the rejection over claim 32 is obviated, that the rejection over claim 40 is obviated as well.

Claims 44, 46, 48, 55, 56, 62 and 64 stand rejected under 53 U.S.C. § 103(a) as purportedly unpatentable over Lowy, Hagensee, Borysiewicz, Galloway, and Meyer, as further evidenced by Boursnell, and further in view of Bubenik et al. (International Journal of Oncology. 1996; 8: 447-481) ("Bubenik").

The Office states that expressing the IL-2 in an expression vector to avoid multiple administrations would have been knowledge generally available to one of ordinary skill in the art. The Office further argues that the skilled artisan would have been motivated to incorporate the IL-2 of Bubenik into the MVA vaccinia vector of Meyer expressing prophylactic L1 and L2 polypeptides of Lowy and Galloway, and the therapeutic E6 and E7 polypeptides of Borysiewicz and Galloway, to augment the immune response to the papillomavirus polypeptides. Applicants traverse.

Bubenik does not remedy the deficiencies of the other references as discussed above. Bubenik discloses a therapeutic strategy which involves administration of HPV-16 infected tumor cells and separate and repeated injections of recombinant IL-2. The animals vaccinated with irradiated cells plus IL-2 were protected to a greater extend than animals only treated with irradiated cells. In the last paragraph, Bubenik proposes a cellular approach to human cervical carcinoma which relies on administration of irradiated tumor cells and IL-2. Applicants' invention is different from this concept set forth in Bubenik, as Applicants claim a single MVA vector co-expressing four papillomavirus polypeptide genes and IL-2, each being placed under independent promoters.

Moreover, it is well known in the art that the timing and schedule of injections are key criteria for therapeutic efficacy, and this concept does not appear to have been considered by the Office. Bubenik recommends separate and repeated injections of IL-2 at the site of vaccination. Bubenik provides no teaching or even

any suggestion otherwise. For example, page 478 states, "In this communication, we have studied the possibility to augment the resistance-inducing effect of hamster K3/II cell line transformed with and expressing transfected HPV E6-E7 genes by IL-2 injected repeatedly at the site of vaccination". Further, on page 480, first column, states "It has been shown, for the first time, in this study, that murine recombinant IL-2 injected repeatedly at the site of vaccination in hamsters immunized with HPV16 E6-E7-transformed and expressing hamster cells can substantially increase the protective efficacy of the vaccine directed against these cells". Twenty repeated injections of IL-2 are indeed required to experimentally observe an adjuvanting effect when administered with irradiated tumor cells.

Thus, the skilled artisan would not have equated the Bubenik approach requiring infection of irradiated tumor cells and repeated administration of IL-2 with that of the present invention requiring administration of a single MVA vector co-expressing four papillomavirus polypeptides and IL-2, or had any expectation of success. In other words, any adjuvanting effect resulting from repeated injections of IL-2 at the site of vaccination did not translate into success a therapeutic response against HPV resulting from administration of a single MVA vector expressing IL-2 together with L1, L2, E6 and E7 papillomavirus polypeptides. Thus, Bubenik does not remedy the deficiencies of the other references, and there is no suggestion in Bubenik to even try the use of IL-2 encoding gene, and even less including the IL-2 gene sequences in the vehicle expressing papillomavirus polypeptides.

Further, Applicants note that the art recognizes that expression of four gene sequences in a single vaccinia virus vector may be problematic. Therefore, the difficulty is even more marked when simultaneous expression of a fifth gene has to be achieved. The skilled artisan at the time the invention was made would not have

had any reasonable expectation of expressing four papillomavirus polypeptides and an additional IL-2 polypeptide in a single MVA vector, each gene being placed under independent regulatory elements. Contrary to the Office's assertion, additional expression of the IL-2 gene in the papillomavirus polypeptide-expressing MVA vector can not be considered as a routine experimentation.

Claim 49 stands rejected under 53 U.S.C. § 103(a) as purportedly unpatentable over Lowy, Hagensee, Borysiewicz, Galloway, and Meyer, as further evidenced by Boursnell and Bubenik and further in view of Crook and Munger.

Claim 49 is a dependent claim referring back to claim 48. Applicants refer to the comments above, submitted on behalf of the rejection of claim 48. Thus, as the rejection over claim 48 is obviated, that the rejection over claim 49 is obviated as well.

Claims 65, 69, 71, 72, 74, 79 and 80 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Borysiewicz, Meyer and Bubenik (, as further evidenced by Boursnell. Borysiewicz disclose a composition comprising a vaccinia virus vector expressing fused HPV-16 E6/E7 coding sequences in the absence of immunostimulator. Meyer is used here as a background reference relating to MVA virus. Bubenik disclose that IL-2 induces an adjuvanting effect when huge quantities of IL-2 are administered repeatedly in combination with irradiated HPV-transformed tumor cells. Boursnell provides experimental work involving expression of two expression cassettes expressing respectively HPV-16 and HPV-18 E6/E7 fusion proteins in a vaccinia virus vector.

However, Borysiewicz fail to disclose or suggest the inclusion of a polypeptide having immunostimulatory activity which is IL-2, IL-7 or B7.2 activity in the E6 and E7-expressing MVA vector and fail to teach or suggest independent expression of teach of the HPV and immunostimulator gene sequences. As discussed above, the Bubenik approach which requires repeated injections of IL-2 at the site of vaccination does not equate direct administration of a MVA vector co-expressing E6 and E7 papillomavirus polypeptides and a polypeptide having immunostimulatory activity such as IL-2. Boursnell et al. recognize that expression of more than two independent expression cassettes can be problematic in vaccinia virus vectors and recommend fusion of the coding sequences to obviate such difficulties. Meyer et al. emphasize a number of differences in terms of cell infection and genome between the MVA and wild-type vaccinia viruses.

As discussed above, there is no suggestion or motivation in any of the cited references or the knowledge available to the skilled artisan to combine the disclosures of the cited references in order to arrive at the claimed composition and method with a reasonable expectation of success.

Claim 75 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Borysiewicz, Meyer and Bubenik and further in view of crook et al. and Munger as further evidenced by Boursnell.

Claim 75 is a dependent claim referring back to claim 65. Applicants refer to the comments above, submitted on behalf of the rejection of claim 65. Thus, as the rejection over claim 65 is obviated, that the rejection over claim 75 is obviated as well.

CONCLUSION

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,

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